**Department of Health and Human Services**

Public Health Service
Food and Drug Administration
Atlanta District Office
60 8th Street, N.E.
Atlanta, Georgia 30309

March 25, 2008

**VIA FEDERAL EXPRESS**

Jean-Pierre Garnier, Ph.D.
Chief Executive Officer
GlaxoSmithKline
Five Moore Drive
Research Triangle Park, NC 27709

**WARNING LETTER**
(08-ATL-05)

Dear Dr. Garnier:

On August 20 through November 13, 2007, an inspection was conducted at your corporate headquarters, located at Five Moore Drive in Research Triangle Park, NC, by the United States Food and Drug Administration (FDA). The inspection focused on your firm's compliance with Postmarketing Adverse Drug Experience (PADE) reporting requirements and other postmarketing reporting requirements relating to Avandia (rosiglitazone maleate), approved by FDA on May 25, 1999, under NDA 21-071.

Our inspection revealed that your firm failed to report data relating to clinical experience, along with other data and information, for Avandia, as required under Section 505(k)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 355(k)(1)] and Title 21 of the Code of Federal Regulations (21 CFR) Sections 314.80 and 314.81. In particular, the inspection found that your firm failed to report multiple postmarketing studies involving Avandia in mandatory Periodic and/or NDA Annual Reports. Failure to comply with Section 505(k) of the Act is a prohibited act under Section 301(e) of the Act [21 U.S.C. § 331(e)].

The deviations observed during the inspection demonstrating your firm's failure to comply with 21 CFR §§ 314.80 and 314.81 include the following:

1) Not all of your firm's Periodic Reports contained a history of actions taken because of adverse drug experiences since the last adverse drug experience report, as required by 21 CFR § 314.80(c)(2)(ii)(c). Specifically, the 2001 Periodic Report for Avandia, NDA 21-071, was incomplete because your firm failed to include information concerning the initiation of the 49653/211 and RECORD studies.

2) Not all of your firm's Annual Reports contained a status report for all postmarketing studies being performed by, or on behalf of, GlaxoSmithKline (GSK) as required by 21 CFR § 314.81(b)(2)(viii). Specifically, the following NDA Annual Reports for Avandia, NDA 21-071, were not complete because your firm failed to include the referenced studies:

- 2001 NDA Annual Report - studies 49653/211 and 105704
- 2002 NDA Annual Report - studies 49653/211, RECORD, and 105704
- 2003 NDA Annual Report - studies RECORD, 105704, and 49653/410

• 2004 NDA Annual Report - studies 49653/211, RECORD, 105704, 49653/410, and AVA100193

• 2005 NDA Annual Report -studies 49653/211, APPROACH, ARA102198, 105704, 49653/410, AVA100193, AVA100468, AVS101946, BRL49653/461, and AVA100930

• 2006 NDA Annual Report - studies AVD104742, AVD105720, AVD102209, RES104033, RES104385, ARA102198, 105704, 49653/410, AVA100193, AVA100468, AVS101946, AVS102130, AVS103888, BRL49653/461, and AVA100930

• 2007 NDA Annual Report - studies RECORD, APPROACH, AVD 104742, AVD105720, AVD105248, AVD102209, RES104033, RES104385, ARA102198, 105704, 49653/410, AVA100193, AVA100468, AVS101946, AVS102130, AVS103888, BRL49653/461, and AVA100930. In fact, entire sections were missing from the 2007 Annual Report such as "Status of Postmarketing Study Commitments" and "Status Studies." of Other Postmarketing Studies."

3) Not all of your firm's Annual Reports contained the status of each postmarketing study concerning clinical efficacy required by FDA or which your firm has committed to conduct, as required by 21 CFR § 314.81(b)(2)(vii). Specifically, the 2007 NDA Annual Report for Avandia, NDA 21-071, was not complete because your firm failed to include information on the ADOPT study.

Although the ADOPT, 49653/211, RECORD, APPROACH, AVA100193, AVA100468, AVS101946, AVS102130, AVS103888, BRL49653/461, and AVA100930 studies were not included in the mandatory NDA annual reports, we acknowledge that they were disclosed in other reports and/or notifications to FDA.

We do not have any evidence showing that the AVD104742, AVD105720, AVD105248, AVD102209, RES104033, RES104385, ARA102198, 105704, or 49653/410 studies were reported to the FDA in any reports and/or notifications prior to the amendment to the 2007 NDA Annual Report that was submitted to FDA on September 26, 2007.

The above postmarketing reporting deviations were listed on the Inspectional Observations (Form FDA 483) issued to and discussed with Dr. Edward N. Pattishall, Vice President, Clinical Safety, at the conclusion of the inspection. A copy of this Form FDA 483 is included for your review.

We acknowledge receipt of the December 11, 2007, response from Dr. Pattishall to the Form FDA 483. This response is inadequate because it does not explain how your firm will ensure that it has submitted to FDA all mandatory postmarketing reporting information concerning its approved drug products. FDA's inspection revealed that your firm lacked appropriate knowledge of the studies associated with Avandia, resulting in the reporting deficiencies noted. Absent a clear explanation of the extent and cause of these deficiencies and an adequate plan to correct them, we are concerned that similar deficiencies in the postmarket reporting for your firm's other FDA-approved drugs may exist . We expect that your corrective actions will include a comprehensive evaluation of your firm's reporting of postmarketing studies for all drug products for which your firm holds an approved application.

GSK's response to Form FDA 483 Observation 1 states that GSK was not required to include studies 49653/211 and RECORD in the 2001 Periodic Report for Avandia because these studies were not initiated in response to postmarketing adverse drug experiences. Instead, they were begun at the request of European regulatory authorities as postmarketing commitments to facilitate approval. The response acknowledged that "these studies did focus on safety issues" relating to Avandia. The requirements of 21 CFR § 314.80(c)(2)(ii) state that each periodic report is required to contain "a history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated)." We understand that these actions (studies) were not voluntarily undertaken, and were initiated at the request of European regulatory authorities as postmarketing commitments. The regulations only establish as a condition for reporting that an action be taken because of adverse drug experiences (ADEs), without regard to who requested that the action be taken. Moreover, the intent of this section of the regulations (as described in the preamble for 50 FR 7452) clearly shows that the purpose of periodic reports is to provide safety information to the agency the preamble states "These [periodic] reports are designed to. Specifically, ... present an overview of all the safety-related information learned during that quarter or year .... FDA believes that this safety profile overview will improve the agency's ability to spot drug safety trends." Thus, the requirement for reporting is based on *why* the actions were taken (e.g., because of adverse drug experiences and/or safety concerns), not *who* triggered the actions.

During our evaluation of studies 49653/211 and RECORD, we found that the protocols for these studies

clearly identify adverse drug experiences as concerns that triggered the implementation of these studies. Specifically, the "Rationale" section of the protocol for study 49653/211 states, "Rosiglitazone (like other thiazolidinediones) causes a *mild increase in plasma volume. [emphasis added]* An increase in plasma volume might aggravate existing cardiac failure unless appropriate diuretic therapy is initiated . . . . This study will investigate the effect of rosiglitazone in addition to background anti-diabetic therapy on cardiac structure and function and cardiovascular morbidity and mortality in type 2 diabetic patients with pre-existing CHF [congestive heart failure] (NYHA grade I/II). . . ." The "Rationale" section of the protocol for the RECORD study states, "It [rosiglitazone] also *increases body weight* (albeit without altering known weight-associated cardiovascular risk factors), has a *multifactorial effect on lipids* (some effects putatively beneficial, *some putatively adverse*), and leads to a modest *increase in plasma volume* .... There is a need formally to evaluate long term cardiovascular outcome, both for those who receive the most widely used oral combination therapy (sulphonylurea (SU) plus metformin (MET)), and for those who are given rosiglitazone in addition to their first-line therapy (metformin or SU)." *[emphasis added]*

Regardless of the fact that European regulatory authorities requested that you conduct these studies, they were targeted safety studies that were initiated because of adverse drug experiences and, therefore, met the regulatory requirement for inclusion in the periodic report.

The specific violations noted in this letter are serious and may be symptomatic of underlying postmarketing safety reporting failures. Neither this letter nor the observations noted on the Form FDA 483 are intended to be an all-inclusive list of deficiencies that may exist at your firm. It is your responsibility to ensure adherence to each requirement of the Act and its regulations. FDA expects applicants to report data relating to clinical experience, along with other data or information, for drugs for which an approved application is in effect in accordance with Section 505(k)(1) of the Act [21 U.S.C. § 355(k)(1)] and 21 CFR §§ 314.80 and 314.81.

You should take prompt action to correct the violations described above. Failure to do so may result in regulatory action without further notice. These actions may include, but are not limited to, seizure and/or injunction.

Other federal agencies may take this Warning Letter into account when considering the award of contracts. In addition, any pending New Drug Applications, Abbreviated New Drug Application, or export certificate requests submitted by your firm may not be approved until the above violations are corrected.

Please respond to this office in writing within fifteen working days of receipt of this letter. Your response should describe specific actions that you will take to correct the violations described above. Your response should explain how each action being taken will prevent recurrence of similar violations and how you are able to ensure that your firm has submitted to FDA all mandatory postmarketing reporting information concerning its approved drug products. If corrective actions cannot be completed within fifteen working days, state the reason for the delay and the timeframe within which corrective actions will be completed.

Your response should be sent to Philip S. Campbell, Compliance Officer, at the address noted in the letterhead. If you wish to discuss this letter, you should contact Mr. Campbell at (404) 253-1280.

Sincerely yours,

/S/

Mary H. Woleske, Director
Atlanta District

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